REMARKS

The pending claims in the above-noted application stand rejected in an Office Action mailed February 19, 2008.

Claim 1 has been amended to more specifically direct the claim to Applicant's invention. Claim 42 has been amended to be an independent claim, with all claim limitations from claims 1 and 36 now recited in the body of claim 42.

Rejection under 35 USC § 112

The Examiner has rejected claims 1-3, 5, 7-17, 19-28, 33-36, 42, 44-45, 47, 90-91 and 95 under 35 USC § 112, second paragraph for indefiniteness for failing to point out or distinctly claim the inventive subject matter. Specifically, the Examiner alleges that claim 1 is indefinite because it refers to sequences that are complementary to one of SEQ ID NO's: 1 or 3.

The claim indicates that the HSV "encodes" an antisense to the SCCRO oncogene, and the claims indicate that the nucleic acid encodes a sequence having identity to a nucleotide sequence complementary to SEQ ID No.1 or 3 (or the mRNA transcript thereof) or its complement.

Thus the nucleic acid can be SEQ ID No.1 or 3 (or the mRNA transcript thereof) or its complement.

HSV has a double stranded DNA genome, hence an encoded 'sense' sequence will be present with its complementary 'antisense' sequence, and reference to one provides a clear definition of the other (i.e. of its complement).

The structure of the claimed asSCCRO is therefore not at all inconsistent or ambiguous because the nucleic acid contained in the genome is double stranded DNA and hence can be defined accurately, clearly and without ambiguity, by referring to either strand.

Reconsideration is respectfully requested.

Rejections under 35 U.S.C. § 103(a)

1. Echeverri in view of Rampling et al., Burton et al.,and Gloriso et al.

The Examiner has rejected claims 1-3, 5, 7-17, 33-36, 42, 44-45, 47, 90-91 and 95 under 35 U.S.C. § 103(a), as unpatentable over Echeverri et al. (US 2004/0048277) in view of

Rampling et al. (*Gene Therapy*, 2000, 7:859-866), Burton et al. (*DNA and Cell Biology*, 2002, 21:915-936), and Glorioso et al. (WO 98/51809).

The Examiner contends Echeverri et al. teach SEQ ID NO:12 (which comprises SEQ ID NO:1 of the instant claims) and that antisense polynucleotide sequence of SEQ ID NO:12 inserted into a therapeutically useful viral vector is suitable for therapeutic purposes, especially tumors and cancers. The Examiner contends that the deficiency of Echeverri et al., i.e., failing to teach that the therapeutically usable viral vector is a non-neurovirulent herpes simplex virus, may be remedied by Rampling (allegedly teaching the ICP34.5 deleted HSV1716 strain), Burton (allegedly teaching that genetic manipulation of HSV-1 vectors is relatively straightforward) and Glorioso et al. (allegedly teaching that a mutant HSV virus can be engineered by inserting a pharmacologically active therapeutic polynucleotide within the HSV genome via homologous recombination procedure).

The Examiner contends that one of ordinary skill in the art would have been motivated "to combine the anticancer agent HSV1776 [sic-should be HSV1716] with the anticancer agent nucleic acid that is complementary to SEQ ID NO:1 of the instant case in such a way that the antisense nucleic acid is inserted into the HSV1776[sic]." Office Action, page 6.

Responsive to the rejection, Applicants dispute that skilled artisan would have a "reasonable expectation of success" from the combination of Echeverri et al. in view of Rampling et al., Burton et al., and Glorioso et al. for the instant invention. Applicants in particular wish to bring to the Examiner's attention art-recognized knowledge rebutting the Examiner's alleged *prima facie* case resulting from alleged "reasonable expectation of success" obtainable from the cited references. Specifically, there was an art-recognized difficulty in attaining stable mRNA transcripts in lytic HSV-infected cells in view of the *vhs* nuclease expressed by lytic HSV-infected cells, constituting a "teaching away" from the utility of lytic HSV as a delivery vehicle for antisense.

The existence of a number of individual elements of the invention in the prior art is not in dispute. Applicant had noted the existence and potential utility of non-neurovirulent HSV-1 as a gene delivery vector in the present application (e.g. 2nd paragraph under "Background to the Invention"). The present application also acknowledges the "Oncoseq" SCCRO allele to be a known oncogene.

However, the selection and combination of these elements to provide an efficacious and viable viral gene delivery agent would not have been considered achievable with a reasonable expectation of success when one takes account of the art-recognized problem posed by the existence of the *vhs* gene in the viral genome.

The presence and effect of the *vhs* gene is explained in the section bridging pages 11 and 12 of Applicant's 24 January 2008 response to the previous office action, with reference to Everly et al., which is incorporated into the Applicants' instant response by reference. Applicants' arguments and evidence related to the teachings of Everly et al. do not appear to have been considered by Examiner when preparing the present office action. For the Examiner's convenience, Applicants will re-present the facts and argument hereinbelow.

Viruses according to the present invention are lytic viruses meaning that they are capable of lysis of cells. In particular, they are "oncolytic" meaning that they have the special property of being able to selectively lyse tumour cells. Following infection of a tumour cell, an oncolytic herpes simplex virus begins the process of viral replication and lysis of the cell. Owing to the complexity and diversity of tumours one cannot expect an oncolytic virus to achieve 100% selective destruction of a tumour or neoplastic tissue. It is therefore desirable to find ways of improving the chemotherapeutic properties of oncolytic viruses.

The present invention is concerned with one approach to improving the chemotherapeutic effect of oncolytic HSV by expressing an antisense nucleic acid sequence targeting the SCCRO oncogene from the virus. In addition to helping destroy the tumour cell infected by the HSV, expression of the antisense SCCRO may be useful in destroying and suppressing cells that are not infected, or are poorly infected, by the HSV such as surrounding tumour and non-tumour cells (e.g. cells that are undergoing neoplastic transformation or are supporting growth and spread of the tumour).

Owing to the oncolytic nature of the virus, many tumour cells infected with the virus will be undergoing lysis, meaning that the cellular machinery responsible for transcription is being destroyed – which of itself teaches against expression of high levels of antisense SCCRO nucleic acid. If the antisense nucleic acid is going to be produced to a sufficient level to provide an additive therapeutic effect it must be produced very quickly following infection of the tumour cell with the HSV.

However, the HSV vector genome also encodes the *vhs* gene (UL41), which is active during lytic infections. This gene is well established to degrade both viral and host mRNAs in non-selective fashion – see for example the abstracts of Everly et al., Schmidt Pak et al., (*Virology* 211, 491-506 (1995)), Sarma et al., (*Journal of Virology*, July 2008, p.6600-6609), Strom and Frenkel (*Journal of Virology*, July 1987, p.2198-2207) (These and other relevant *vhs*-related publications, some not discussed herein, are co-submitted with the instant response in an IDS).

For example:

> "During lytic infections, the virion host shutoff (Vhs) protein (UL41) of herpes simplex virus destabilises host and viral mRNAs." Everly et al (abstract)

Schmidt Pak et al., (*Virology* 211, 491-506 (1995)) describe how expression of a CAT reporter gene mRNA was diminished to below measurable levels by the presence of *vhs* (UL41) (see e.g. page 500 right col. 3rd paragraph).

vhs activity appears to be highest during the immediate early stage (the earliest stage) of HSV gene replication. This is indicated in Smibert and Smiley (*Journal of Virology*, August 1990, p.3882-3894, also co-submitted) which describes a herpes simplex virus that expresses beta-globin. During infection of MEL cells that constitutively express beta-globin the cellular beta-globin was rapidly degraded following infection. The virally encoded beta-globin was expressed as an early stage protein (i.e. expressed later than the immediate early proteins) by which time the *vhs* activity was diminishing allowing expression of the viral beta-globin (Discussion p 3890-3892).

The art teaches, therefore, that the *vhs* gene poses a special problem to HSV vector based gene therapy where the vector is a **lytic** vector because the process of cell lysis leaves a very small window of time for production of the therapeutic 'gene'. This window of time coincides with the immediate early expression of the *vhs* gene and associated degradation of mRNA.

The problem is potentially even more acute where the therapeutic 'gene' is an antisense molecule, rather than a protein. For example, an antisense approach requires one antisense transcript to hybridise with one target transcript and at least about 90% of the target transcripts will normally need to be inactivated for protein production to be significantly impaired. In contrast, for expression of a transgenic protein a single transcript can provide for the production of many protein molecules.

Where a virus according to the invention infects a cell containing, for example, 100 SCCRO mRNA molecules the virus must be capable of producing at least 90, preferably 100, antisense SCCRO molecules to prevent SCCRO protein oncogene expression. As demonstrated in Everly et al., Schmidt Pak et al., Sarma et al., and Strom and Frenkel (as well other documents cited) the *vhs* gene will degrade a significant amount, and in some cases virtually all, of the mRNA molecules produced. Such references indicate a "teaching away" from the instant invention.

When one takes account of the presence and effect of the *vhs* gene, one of skill in the art recognizes that it is unpredictable whether, in the short amount of time between infection and lysis of a tumour cell, sufficient antisense SCCRO molecules will be transcribed in order to provide a therapeutic effect that is additive to lysis of the tumour cell.

The person of ordinary skill in the art knew at the filing date of the application that an HSV viral vector encodes *vhs* gene activity that will act immediately after infection to degrade both cellular and viral mRNA. The person of ordinary skill in the art would also understand that in an oncolytic virus a narrow time window is available in which to generate high levels of antisense nucleic acid, and that this time window coincides with *vhs* activity that acts to degrade both viral and cellular mRNA molecules, including antisense nucleic acid. Thus the person of ordinary skill understood it to be at the very least unpredictable as to whether it is possible to produce high levels of the antisense nucleic acid, and indeed success would have been quite surprising.

A person of ordinary skill in the art would therefore have concluded that a reasonable expectation of success could not exist for the production of sufficient SCCRO antisense nucleic acid from an oncolytic herpes simplex virus to provide an additive therapeutic effect, due to the presence of *vhs* gene activity in HSV-1.

In contrast, the application shows, e.g. Example 4 and page 76 middle paragraph together with Figures 20 and 21, that all mice injected with oncolytic HSV expressing the antisense SCCRO nucleic acid showed complete responses by 21 days compared with 50% of mice injected with oncolytic HSV showing complete responses after 48 days. This additive result is surprising and could not have been predicted with a reasonable expectation of success.

In summary, in light of the art describing the destabilization of mRNA transcripts in the HSV-1 virion, with specific example provided (CAT reporter gene mRNA was diminished to

below measurable levels by the presence of *vhs*), it is submitted that there can be no reasonable expectation of success for an additive therapeutic effect for antisense SCCRO molecules, as is claimed in the invention. Further diminishing any expectation of success, Applicants note that there is an additional technical challenge posed by antisense technology. Specifically, for antisense, a higher number of mRNA transcripts are required for antisense activity than for protein transcription, for the reason that transcripts are used once for antisense whereas they may be reused multiple times by transcription machinery for transcription.

Reconsideration is respectfully requested.

2. Echeverri in view of Rampling et al., Burton et al., and Gloriso et al. further in view of Jacobs et al.

The Examiner has rejected claims 1-3, 5, 7-17, 19-28, 33-36, 42, 44-45, 47, 90-91 and 95 under 35 U.S.C. § 103(a), as unpatentable over Echeverri et al. (US 2004/0048277) in view of Rampling et al. (*Gene Therapy*, 2000, 7:859-866), Burton et al. (*DNA and Cell Biology*, 2002, 21:915-936), and Glorioso et al. (WO 98/51809), and further in view of Jacobs et al. (Human *Gene Therapy*, 2003, 14:277-297).

Responsive to the rejection, Applicants dispute that skilled artisan would have a "reasonable expectation of success" from the combination of Echeverri et al. in view of Rampling et al., Burton et al., and Glorioso et al., further in view of Jacobs et al., for the instant invention. Applicants reference arguments made above in the section relating to the rejection over Echeverri et al. in view of Rampling et al., Burton et al., and Glorioso et al. Summarizing the Applicant's above argument, it is submitted that a person of ordinary skill in the art would have concluded that a reasonable expectation of success could not exist for the production of sufficient SCCRO antisense nucleic acid from an oncolytic herpes simplex virus to provide an additive therapeutic effect, due to the presence of *vhs* gene activity in HSV-1.

Jacobs is cited in additional combination to each of the above rejections. The Examiner alleges that this teaching arises to the level of a "proof of principle" vector system. See Office Action, page 8. Applicants respectfully submit that success with protein expression from a non-lytic amplicon vector (Jacobs et al.) in fact is non-applicable regarding any expectation of success of antisense expression from a lytic HSV viral vector (the instant invention). Applicants submit that the system taught in Jacobs et al. is based on HSV amplicon vectors, not HSV viral

vectors, differing in that the Jacobs et al. constructs are not lytic, do not contain genetic material encoding the *vhs* gene, and use a different (cytomegalovirus) promoter.

Jacobs et al. is concerned with HSV-1 amplicon vectors for protein expression. These artificial non-viral vectors contain a small subset of HSV-1 genes to facilitate replication of the amplicon DNA. The structure of the amplicons is shown in Figure 1. The amplicon vectors are non-lytic expression vectors. Thus when considering gene expression from an amplicon vector the problem of concurrent cell lysis is not a factor meaning that the amplicon vector system is not required to achieve gene expression in a short time window following infection of the cell. The amplicons incorporate the cytomegalovirus promoter (pCMV) which is a strong constitutive promoter. In order to package the amplicon DNA, Vero cells were cotransfected with *Pac*I digested HSV-1 cosmid DNA and the HSV-1 amplicon plasmid (Jacobs at page 281 left col. - "Helper virus-free packaging of HSV-1 amplicons"). Expression of the cosmid DNA provides the cell with functions required to package the amplicon DNA into a viral particle. The packaged amplicon particle does not contain genetic material encoding the *vhs* gene. Thus upon infection of the cell immediate early *vhs* gene expression does not occur to inhibit viral and host mRNA expression. Given that the amplicon is non-lytic and the gene of interest is under control of a constitutive promoter, even if *vhs* activity was present in the amplicon particle and caused an inhibition of immediate early stage gene expression the cell would be expected to remain intact and allow expression of the gene of interest from the early or later stages of gene expression (e.g. as described for beta-globin in Smibert and Smiley (*Journal of Virology*, August 1990, p.3882-3894).

Thus Jacobs et al. is not predictive of the effect of *vhs* gene activity on the level of mRNA produced by an expression vector at the immediate early stage of infection, which is the relevant consideration for a lytic virus of the kind claimed in the instant application. Jacobs is also not concerned with a viral vector, but an artificial plasmid-type amplicon vector, and thus is also not predictive of the complexity of the interactions of the protein functions encoded by the HSV-1 viral genome and how they might affect RNA expression.

Also rebutting the Examiner's alleged "proof of principle" for the HSV vector system, is the art relating to *vhs* activity as discussed herein above. Specifically, Schmidt Pak et al., (*Virology* 211, 491-506 (1995)) describe how expression of a CAT reporter gene mRNA was diminished to below measurable levels by the presence of *vhs* (UL41) (see e.g. page 500 right

col. 3rd paragraph). Note the existence of a large number of references discussing the destabilization of mRNA of both host and virion mRNAs during infection (Elgadi et al., *Journal of Virology*, Vol. 73, No. 9 (p. 7153-7164) (1999) ("vhs destabilizes most if not all of the viral and cellular mRNAs during infection.")

As noted above, the problem is potentially even more acute where the therapeutic 'gene' is an antisense molecule, rather than a protein. For example, an antisense approach requires one antisense transcript to hybridize with one target transcript and at least about 90% of the target transcripts will normally need to be inactivated for protein production to be significantly impaired. In contrast, for expression of a transgenic protein a single transcript can provide for the production of many protein molecules. However, as demonstrated in Everly et al., Schmidt Pak et al., Sarma et al., and Strom and Frenkel (as well other documents cited) the *vhs* gene will degrade a significant amount of the mRNA molecules produced.

When one takes account of the presence and effect of the *vhs* gene, one realises that it is unpredictable whether that in the short amount of time between infection and lysis of a tumour cell sufficient antisense SCCRO molecules will be transcribed in order to provide a therapeutic effect that is additive to lysis of the tumor cell.

In light of the art describing the destabilization of mRNA transcripts in the HSV-1 virion, with specific example provided (CAT reporter gene mRNA was diminished to below measurable levels by the presence of *vhs*), it is submitted that there is no reasonable expectation of success for an additive therapeutic effect for antisense SCCRO molecules, as is claimed in the invention. Further diminishing any expectation of success, Applicants note that there is an additional technical challenge posed by antisense technology. Specifically, for antisense, a higher number of mRNA transcripts are required for antisense activity than for protein transcription, for the reason that transcripts are used once for antisense whereas they may be reused multiple times by transcription machinery for transcription. Applicants respectfully submit that success with protein expression from a non-lytic amplicon vector (Jacobs et al.) in fact is non-applicable regarding any expectation of success of antisense expression from a lytic HSV viral vector (the instant invention). For that reason, it is submitted that any "proof of principle", should consist of demonstrated antisense functionality in HSV-1.

Reconsideration is respectfully requested.

3. Lodes et al. in view of Rampling et al., Burton et al. and Glorioso et al.

The Examiner has rejected claims 1-3, 5, 7-17, 33-36, 42, 44-45, 47, 90-91 and 95 under 35 U.S.C. § 103(a), as unpatentable over Lodes (WO 200052165) in view of Rampling et al. (*Gene Therapy*, 2000, 7:859-866), Burton et al. (*DNA and Cell Biology*, 2002, 21:915-936) and Glorioso et al. (WO 98/51809).

The Examiner contends that the instant specification teaches at least a 20 nucleotide "fragment" and that Lodes teaches a polynucleotide sequence SEQ ID NO:91 which corresponds to nucleotides 53-492 of SEQ ID NO:1 of the instant invention, and that Lodes teaches an antisense polynucleotide of SEQ ID NO:91 useful to treat breast cancer. The Examiner contends that although Lodes does not teach a non-neurovirulent herpes simplex virus, Loes teaches that techniques for incorporating DNA into a viral vector are well known in the art. The Examiner contends that Rampling et al. teaches the ICP34.5 deleted HSV 1716 strain has been shown to be effective in human cancer in preclinical settings; that Burton teaches that various types of HSV-1 vectors have been widely used as gene therapy vectors; that Glorioso et al. teach that a mutant HSV virus can be engineered by inserting a pharmacologically active therapeutic polynucleotide including an antisense RNA. The Examiner contends that it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the anticancer agent HSV1776 [sic-should be HSV 1716] with the antisense cancer agent nucleic acids as claimed, and that one of ordinary skill would be motivated to do so with a reasonable expectation of success.

Responsive to the rejection, Applicants dispute that skilled artisan would have a "reasonable expectation of success" from the combination Lodes et al. in view of Rampling et al., Burton et al. and Glorioso et al. As discussed hereinabove, and incorporated by reference into this paragraph, Applicants wish to bring to the Examiner's attention art-recognized knowledge rebutting the Examiner's alleged *prima facie* case resulting from alleged "reasonable expectation of success" obtainable from the cited references. Specifically, there was an art-recognized difficulty in attaining stable mRNA transcripts in lytic HSV-infected cells in view of the *vhs* nuclease expressed by lytic HSV-infected cells, constituting a "teaching away" from the utility of lytic HSV as a delivery vehicle for antisense.

As discussed for the rejections headed by Echeverri et al. above and summarized herein (and incorporated herein), the existence of a number of individual elements of the invention in

the prior art is not in dispute. However, the selection and combination of these elements to provide an efficacious and viable viral gene delivery agent would not have been considered achievable with a reasonable expectation of success when one takes account of the art-recognized problem posed by the existence of the *vhs* gene in the viral genome.

Viruses according to the present invention are "oncolytic" meaning that they have the special property of being able to selectively lyse tumour cells. The present invention is concerned with one approach to improving the chemotherapeutic effect of oncolytic HSV by expressing an antisense nucleic acid sequence targeting the SCCRO oncogene from the virus. Owing to the oncolytic nature of the virus, many tumour cells infected with the virus will be undergoing lysis, meaning that the cellular machinery responsible for transcription is being destroyed – which of itself teaches against expression of high levels of antisense SCCRO nucleic acid. If the antisense nucleic acid is going to be produced to a sufficient level to provide an additive therapeutic effect it must be produced very quickly following infection of the tumour cell with the HSV.

However, the HSV vector genome also encodes the *vhs* gene (UL41), which is active during lytic infections. This gene is well established to degrade both viral and host mRNAs in non-selective fashion – see for example the abstracts of Everly et al., Schmidt Pak et al., (*Virology* 211, 491-506 (1995)), Sarma et al., (*Journal of Virology*, July 2008, p.6600-6609), Strom and Frenkel (*Journal of Virology*, July 1987, p.2198-2207). In particular, Everly et al. teaches: "[d]uring lytic infections, the virion host shutoff (Vhs) protein (UL41) of herpes simplex virus destabilises host and viral mRNAs." Everly et al (abstract). Further, Schmidt Pak et al., (*Virology* 211, 491-506 (1995)) describe how expression of a CAT reporter gene mRNA was diminished to below measurable levels by the presence of *vhs* (UL41) (see e.g. page 500 right col. 3rd paragraph).

vhs activity appears to be highest during the immediate early stage (the earliest stage) of HSV gene replication, as discussed above for the Smibert and Smiley reference. The art teaches, therefore, that the *vhs* gene poses a special problem to HSV vector based gene therapy where the vector is a **lytic** vector because the process of cell lysis leaves a very small window of time for production of the therapeutic 'gene'. This window of time coincides with the immediate early expression of the *vhs* gene and associated degradation of mRNA.

The problem is potentially even more acute where the therapeutic 'gene' is an antisense molecule, rather than a protein. For example, an antisense approach requires one antisense transcript to hybridize with one target transcript and at least about 90% of the target transcripts will normally need to be inactivated for protein production to be significantly impaired. In contrast, for expression of a transgenic protein a single transcript can provide for the production of many protein molecules. As demonstrated in Everly et al., Schmidt Pak et al., Sarma et al., and Strom and Frenkel (as well other documents cited) the *vhs* gene will degrade a significant amount, and in some cases virtually all, of the mRNA molecules produced. Such references indicate a "teaching away" from the instant invention.

When one takes account of the presence and effect of the *vhs* gene, one of skill in the art recognizes that it is unpredictable whether, in the short amount of time between infection and lysis of a tumour cell, sufficient antisense SCCRO molecules will be transcribed in order to provide a therapeutic effect that is additive to lysis of the tumour cell.

The person of ordinary skill in the art knew at the filing date of the application that an HSV viral vector encodes *vhs* gene activity that will act immediately after infection to degrade both cellular and viral mRNA. The person of ordinary skill in the art would also understand that in an oncolytic virus a narrow time window is available in which to generate high levels of antisense nucleic acid, and that this time window coincides with *vhs* activity that acts to degrade both viral and cellular mRNA molecules, including antisense nucleic acid. Thus the person of ordinary skill understood it to be at the very least unpredictable as to whether it is possible to produce high levels of the antisense nucleic acid, and indeed success would have been quite surprising.

In contrast, the application shows, e.g. Example 4 and page 76 middle paragraph together with Figures 20 and 21, that all mice injected with oncolytic HSV expressing the antisense SCCRO nucleic acid showed complete responses by 21 days compared with 50% of mice injected with oncolytic HSV showing complete responses after 48 days. This additive result is surprising and could not have been predicted with a reasonable expectation of success.

In summary, in light of the art describing the destabilization of mRNA transcripts in the HSV-1 virion, with specific example provided (CAT reporter gene mRNA was diminished to below measurable levels by the presence of *vhs*), it is submitted that there can be no reasonable expectation of success for an additive therapeutic effect for antisense SCCRO molecules, as is

claimed in the invention. Further diminishing any expectation of success, Applicants note that there is an additional technical challenge posed by antisense technology. Specifically, for antisense, a higher number of mRNA transcripts are required for antisense activity than for protein transcription, for the reason that transcripts are used once for antisense whereas they may be reused multiple times by transcription machinery for transcription.

Reconsideration is respectfully requested.

4. Lodes et al. in view of Rampling et al., Burton et al. and Glorioso et al., further in view of Jacobs et al.

The Examiner has rejected claims 1-3, 5, 7-17, 19-28, 33-36, 42, 44-45, 47, 90-91 and 95 under 35 U.S.C. § 103(a), as unpatentable over Lodes (WO 200052165) in view of Rampling et al. (*Gene Therapy*, 2000, 7:859-866), Burton et al. (*DNA and Cell Biology*, 2002, 21:915-936) and Glorioso et al. (WO 98/51809), and further in view of Jacobs et al. (*Human Gene Therapy*, 2003, 14:277-292).

The Examiner contends that the combined references of Lodes, Rampling et al., Burton et al., Burton et al., and Glorioso et al. teach a recombinant HSV1716 containing an antisense fragment of SEQ ID NO:1, which is useful for cancer treatment, but do not teach that the recombinant HSV 1716 further includes other functional elements, such as claimed IRES, GFP/EGFP, and SV40 sequences. The Examiner contends that Jacobs et al. teaches genetically engineered HSV-1 vectors containing IRES, GFP/EGFP, and SV40 sequences and teach guidelines as to how to construct engineered HSV-1 vectors, which are alleged to represent "proof of principle" vector systems for gene therapy.

Responsive to the rejection, Applicants dispute that skilled artisan would have a "reasonable expectation of success" from the combination Lodes et al. in view of Rampling et al., Burton et al. and Glorioso et al. in view of Jacobs et al. As discussed hereinabove, and incorporated by reference into this paragraph, Applicants wish to bring to the Examiner's attention art-recognized knowledge rebutting the Examiner's alleged *prima facie* case resulting from alleged "reasonable expectation of success" obtainable from the cited references. Specifically, there was an art-recognized difficulty in attaining stable mRNA transcripts in lytic HSV-infected cells in view of the *vhs* nuclease expressed by lytic HSV-infected cells, constituting a "teaching away" from the utility of lytic HSV as a delivery vehicle for antisense.

Briefly, the selection and combination of the elements present in the instant claims and disclosed in the cited references, to provide an efficacious and viable viral gene delivery agent, would not have been considered achievable with a reasonable expectation of success when one takes account of the art-recognized problem posed by the existence of the *vhs* gene in the viral genome. As discussed hereinabove, owing to the oncolytic nature of the virus, many tumour cells infected with the virus will be undergoing lysis, meaning that the cellular machinery responsible for transcription is being destroyed – which of itself teaches against expression of high levels of antisense SCCRO nucleic acid. If the antisense nucleic acid is going to be produced to a sufficient level to provide an additive therapeutic effect it must be produced very quickly following infection of the tumour cell with the HSV.

However, the HSV vector genome also encodes the *vhs* gene (UL41), which is active during lytic infections. This gene is well established to degrade both viral and host mRNAs in non-selective fashion. The art teaches, therefore, that the *vhs* gene poses a special problem to HSV vector based gene therapy where the vector is a **lytic** vector because the process of cell lysis leaves a very small window of time for production of the therapeutic 'gene'. This window of time coincides with the immediate early expression of the *vhs* gene and associated degradation of mRNA.

The problem is potentially even more acute where the therapeutic 'gene' is an antisense molecule, rather than a protein. For example, an antisense approach requires one antisense transcript to hybridize with one target transcript and at least about 90% of the target transcripts will normally need to be inactivated for protein production to be significantly impaired. In contrast, for expression of a transgenic protein a single transcript can provide for the production of many protein molecules.

Where a virus according to the invention infects a cell containing, for example, 100 SCCRO mRNA molecules the virus must be capable of producing at least 90, preferably 100, antisense SCCRO molecules to prevent SCCRO protein oncogene expression. As demonstrated in Everly et al., Schmidt Pak et al., Sarma et al., and Strom and Frenkel (as well other documents cited) the *vhs* gene will degrade a significant amount, and in some cases virtually all, of the mRNA molecules produced. Such references indicate a "teaching away" from the instant invention.

Jacobs is cited in additional combination to each of the above rejections. This reference is discussed hereinabove, which is incorporated by reference into this rejection. Briefly, Applicants respectfully submit that success with protein expression from a non-lytic amplicon vector (Jacobs et al.) in fact is non-applicable regarding any expectation of success of antisense expression from a lytic HSV viral vector (the instant invention). Applicants submit that the system taught in Jacobs et al. is based on HSV amplicon vectors, not HSV viral vectors, differing in that the Jacobs et al. constructs are not lytic, do not contain genetic material encoding the *vhs* gene, and use a different (cytomegalovirus) promoter. Specifically, Jacobs et al. is concerned with HSV-1 amplicon vectors for protein expression. The amplicon vectors are non-lytic expression vectors. The amplicons incorporate the cytomegalovirus promoter (pCMV) which is a strong constitutive promoter. The packaged amplicon particle does not contain genetic material encoding the *vhs* gene. Thus upon infection of the cell immediate early *vhs* gene expression does not occur to inhibit viral and host mRNA expression.

Thus Jacobs et al. is not predictive of the effect of *vhs* gene activity on the level of RNA produced by an expression vector at the immediate early stage of infection, which is the relevant consideration for a lytic virus of the kind claimed in the instant application. Jacobs is also not concerned with a viral vector, but an artificial plasmid-type amplicon vector, and thus is also not predictive of the complexity of the interactions of the protein functions encoded by the HSV-1 viral genome and how they might affect RNA expression.

Accordingly, when one takes account of the presence and effect of the *vhs* gene, one of skill in the art recognizes that it is unpredictable whether, in the short amount of time between infection and lysis of a tumour cell, sufficient antisense SCCRO molecules will be transcribed in order to provide a therapeutic effect that is additive to lysis of the tumour cell. A person of ordinary skill in the art would therefore have concluded that a reasonable expectation of success could not exist for the production of sufficient SCCRO antisense nucleic acid from an oncolytic herpes simplex virus to provide an additive therapeutic effect, due to the presence of *vhs* gene activity in HSV-1.

In contrast, the application shows, e.g. Example 4 and page 76 middle paragraph together with Figures 20 and 21, that all mice injected with oncolytic HSV expressing the antisense SCCRO nucleic acid showed complete responses by 21 days compared with 50% of mice

injected with oncolytic HSV showing complete responses after 48 days. This additive result is surprising and could not have been predicted with a reasonable expectation of success.

In summary, in light of the art describing the destabilization of mRNA transcripts in the HSV-1 virion, with specific example provided (CAT reporter gene mRNA was diminished to below measurable levels by the presence of *vhs*), it is submitted that there can be no reasonable expectation of success for an additive therapeutic effect for antisense SCCRO molecules, as is claimed in the invention. Further diminishing any expectation of success, Applicants note that there is an additional technical challenge posed by antisense technology. Specifically, for antisense, a higher number of mRNA transcripts are required for antisense activity than for protein transcription, for the reason that transcripts are used once for antisense whereas they may be reused multiple times by transcription machinery for transcription. Applicants respectfully submit that success with protein expression from a non-lytic amplicon vector (Jacobs et al.) in fact is non-applicable regarding any expectation of success of antisense expression from a lytic HSV viral vector (the instant invention).

Reconsideration is respectfully requested.

5. Estilo et al. in view of Rampling et al., Crooke et al. and Jacobs et al.

The Examiner has rejected claims 1-3, 5, 7-17, 19-28, 33-36 42, 44-45, 47, 90-91 and 95 under 35 U.S.C. § 103(a), as unpatentable over Estilo et al. (Clinical Cancer Research, 2003, 9:2300-2306) in view of Rampling et al. (*Gene Therapy*, 2000, 7:859-866), Crooke (Oncogene, 2000, 19:6651-6659) and Jacobs et al. (Human *Gene Therapy*, 2003, 14:277-297).

The Examiner contends that Estilo et al. teach mRNA expression of SCCRO is overexpressed in head neck cancer and may provide a basis for development of anti tumor strategies. The Examiner contends that Rampling et al. teach that the ICP34.5 deleted HSV1716 strain has been shown to be effective in slowing tumor growth. The Examiner contends that Crooke teaches that antisense technology can be useful for cancer treatment. The Examiner contends that Jacobs et al. teach genetically engineered HSV-1 vectors containing IRES, GFP/EGFP, and SV40 sequences and that such HSV-1 vectors containing any therapeutic gene, which allegedly provide "proof of principle" vector systems for gene therapy. The Examiner concludes that one of skill would have motivation for the instant invention based on these references, and states that a *prima facie* case of obviousness has been made out.

Applicants respectfully disagree with the Examiner's conclusions. Specifically, the likelihood of success alleged by the Examiner is rebutted by the art-recognized knowledge of those of skill in the art, as discussed hereinabove, and incorporated by reference herein.

Briefly, it is submitted that a person of ordinary skill in the art would have concluded that a reasonable expectation of success could not exist for the production of sufficient SCCRO antisense nucleic acid from an oncolytic herpes simplex virus to provide an additive therapeutic effect, due to the presence of *vhs* gene activity in HSV-1.

Jacobs et al. is cited in additional combination to each of the above rejections. This reference is discussed hereinabove, which is incorporated by reference into this rejection. Briefly, Applicants respectfully submit that success with protein expression from a non-lytic amplicon vector (Jacobs et al.) in fact is non-applicable regarding any expectation of success of antisense expression from a lytic HSV viral vector (the instant invention). Applicants submit that the system taught in Jacobs et al. is based on HSV amplicon vectors, not HSV viral vectors, differing in that the Jacobs et al. constructs are not lytic, do not contain genetic material encoding the *vhs* gene, and use a different (cytomegalovirus) promoter. Specifically, Jacobs et al. is concerned with HSV-1 amplicon vectors for protein expression. The amplicon vectors are non-lytic expression vectors. The amplicons incorporate the cytomegalovirus promoter (pCMV) which is a strong constitutive promoter. The packaged amplicon particle does not contain genetic material encoding the *vhs* gene. Thus upon infection of the cell immediate early *vhs* gene expression does not occur to inhibit viral and host mRNA expression.

Thus Jacobs et al. is not predictive of the effect of *vhs* gene activity on the level of RNA produced by an expression vector at the immediate early stage of infection, which is the relevant consideration for a lytic virus of the kind claimed in the instant application. Jacobs is also not concerned with a viral vector, but an artificial plasmid-type amplicon vector, and thus is also not predictive of the complexity of the interactions of the protein functions encoded by the HSV-1 viral genome and how they might affect RNA expression.

As noted above, the problem is potentially even more acute where the therapeutic 'gene' is an antisense molecule, rather than a protein. For example, an antisense approach requires one antisense transcript to hybridize with one target transcript and at least about 90% of the target transcripts will normally need to be inactivated for protein production to be significantly

impaired. In contrast, for expression of a transgenic protein a single transcript can provide for the production of many protein molecules.

When one takes account of the presence and effect of the *vhs* gene, one realises that it is unpredictable whether, in the short amount of time between infection and lysis of a tumour cell, sufficient antisense SCCRO molecules will be transcribed in order to provide a therapeutic effect that is additive to lysis of the tumor cell.

In light of the art describing the destabilization of mRNA transcripts in the HSV-1 virion, with specific example provided (CAT reporter gene mRNA was diminished to below measurable levels by the presence of *vhs*), it is submitted that there is no expectation of success for an additive therapeutic effect for antisense SCCRO molecules, as is claimed in the invention. Further diminishing any expectation of success, Applicants note that there is an additional technical challenge posed by antisense technology. Specifically, for antisense, a higher number of mRNA transcripts are required for antisense activity than for protein transcription, for the reason that transcripts are used once for antisense whereas they may be reused multiple times by transcription machinery for transcription. For that reason, it is submitted that any "proof of principle", should consist of demonstrated antisense functionality in HSV-1.

Further, it is submitted that in particular Schmidt Pak et al., showing almost complete degradation of a reporter gene mRNA for HSV-1 virions due to the presence of the *vhs* gene, rebuts any expectation of success a person of ordinary skill might derive from the claimed invention from cited Jacobs et al. The prior art leads to the conclusion that it is unpredictable whether a given gene will result in transcription and the amount of any transcript due to known mRNA instability. As explained above, antisense requirements for greater amounts of mRNA transcripts further weakens the case for predictability.

Reconsideration is respectfully requested.

For the reasons set forth above, Applicant respectfully submits the claims as filed are allowable over the art of record and reconsideration and issuance of a notice of allowance are respectfully requested. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefor to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to deposit account No. 19-5117.

Respectfully submitted,

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Mary Breen Smith, #43,512
Swanson & Bratschun, L.L.C.
8210 Southpark Terrace
Littleton, CO 80120
Telephone: (303) 268-0066
Facsimile: (303) 268-0065

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